UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: NATIONAL PRESCRIPTION OPIATE LITIGATION	MDL No. 2804
THIS DOCUMENT RELATES TO:	Case No. 1:17-md-2804
Track Three Cases	Judge Dan Aaron Polster

REPLY IN SUPPORT OF DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

REPLY EXHIBIT 1

EXPERT REPORT OF KATHERINE KEYES, PHD

August 3, 2020

I. BACKGROUND AND QUALIFICATIONS

A. Summary

I am an Associate Professor of Epidemiology at Columbia University, specializing in substance use and substance use disorders epidemiology.

B. Education

I received a Masters degree in Public Health from Columbia University in 2004, and a PhD in Epidemiology from Columbia University in 2010.

C. Field of specialty and employment history

My field of specialty is substance use and substance use disorders, as well as related comorbidity, focusing on psychiatric disorders, and consequences of substance use including intentional and unintentional injury. After receiving my PhD in Epidemiology in 2010, I completed a post-doctoral fellowship in Epidemiology at Columbia University from 2010 through 2012, and then was recruited by Columbia University to join the faculty in 2012 as a tenure-track Assistant Professor. I was promoted to Associate Professor in 2016, and received tenure at Columba University in 2020. I also hold academic appointments at various other universities. I am a Research Assistant Professor at the University of Michigan, and an Adjunct Associate Professor at the Society for Health and Research at Universidad Mayor in Santiago, Chile.

D. Research areas and publications

I have published 271 peer-reviewed articles, editorials, and book chapters, more than 70 of which are first-authored. Much of this research has been published in the leading, highest impact epidemiology, psychiatry, and substance use journals, including in *Pediatrics, JAMA Psychiatry, Lancet Psychiatry, Nature Communications, British Medical Journal, British Journal of Psychiatry, American Journal of Psychiatry, American Journal of Epidemiology,* and *International Journal of Epidemiology*, among others. My articles have been cited in numerous disciplines, including psychiatry, epidemiology, public health, and pediatrics. My *h*-index ranges from 74[*] on Google Scholar. Currently, 50 of my articles have been cited more than 100 times; 15 of my articles have been cited more than 200 times; and 4 have been cited more than 500 times. Since obtaining my doctoral degree, I have led and sustained numerous grant-funded projects as Principal Investigator, and have successfully competed for grant funding from the National Institutes of Health to conduct my research. I have received numerous grants from Columbia University for my work, including the Calderone Prize for junior faculty, and the Tow scholarship (awarded to high-achieving mid-career scientists). I serve as a co-Investigator on numerous federally-funded projects both at Columbia and at other institutions (including University of Michigan and New York University). In 2019, I was named as a "Highly Cited Researcher" by Web of Science, which recognizes "the world's most influential researchers of the past decade, demonstrated by the production of multiple highly-cited papers that rank in the top 1% by citations for the field and year in Web of Science."

I have published two textbooks on epidemiological methods, and I am well-qualified to assess the literature on opioid-related harm. The first is *Epidemiology Matters: A New Introduction to Methodological Foundations*, published by Oxford University Press in 2014, which is currently being used to teach graduate students about epidemiological methods in more than 20 universities. The second is *Population Health Science*, also published by Oxford University Press, which details the theoretical and methodological foundations of the science of public health.

[*] An *h*-index is a measure of productivity and research impact. It measures the correlation between the number of peer-reviewed papers and the number of times each paper. An *h*-index of 68 indicates that I have published a median of 68 papers that have been cited at least 68 times. Benchmarks for *h*-indices vary; at Columbia University the standards for promotion in the department of epidemiology, are an *h*-index of at least 15 for promotion to Associate Professor, and at least 25 for promotion to professor. My *h*-index is more than twice that needed for a full professor rank in my department at Columbia University, indicative of high productivity and impact.

My expertise on opioid-related harm includes large scale survey data and vital statistics analyses, as well as the development of theories, hypotheses, and publishing findings concerning the role of macro-social factors in producing opioid epidemics. Specifically, I have extensively used high-quality survey data collected at the national level in order to estimate incidence, prevalence, and trends in risk factors for opioid use disorders, and trends in opioid use. Further, I have utilized data on fatal and non-fatal overdose to estimate determinants of variation in overdose across communities. My work focuses on community-based sampling strategies as well as hospital records to document epidemiological correlates and determinants of risk. I have published 21 peer-reviewed journal articles on opioid use and related harms (and many more on drug use disorders more generally), detailing trends over time in prescription opioid misuse, birth cohort trends in nonmedical opioid use and overdose, risk factors for non-medical prescription opioid use, and consequences of use across developmental periods, including consequences related to overdose. I have particularly focused on elucidating drivers of population-level trends, including literature reviews, synthesis, and empirical analyses of urban-rural differences in nonmedical opioid use and overdose. This work is aided by the 2019 inauguration of the Policy and Health Initiatives on Opioids and Other Substances (PHIOS) center at Columbia University based in the department of epidemiology, where I serve as a faculty member and also as a steering committee member of the Substance Abuse Epidemiology Training Program (SAETP), by which I train and mentor doctoral and post-doctoral scholars in substance abuse epidemiology. I am an investigator on the HEALing Communities Study, a large, $350 million dollar NIH-funded initiative aiming to reduce opioid overdose by 40 percent in four states, including New York, Ohio, Kentucky, and Massachusetts through implementation and dissemination of evidence-based prevention and intervention efforts, including expanded access to medication for opioid use disorder, distribution of naloxone to reverse overdose, and efforts to reduce high-risk prescribing. My role on the project is to develop mathematical simulations of the cycle of opioid use in New York State, and to estimate the anticipated reduction in overdose deaths by simulating combinations of intervention initiatives taking into account the system dynamics of counties in New York State. I am also a co-investigator of an NIH grant-funded project focused on estimating the impact of policies that target opioid use (e.g., prescription drug monitoring programs, prescribing and clinic laws, Good Samaritan laws, etc.) on opioid and benzodiazepine co-prescribing and overdose. Thus, I am well-qualified to review the literature and offer opinions based on the evidence and my own experience. I have no conflicts of interest in making these assessments, and have never consulted on behalf of any entities that stand to profit from drug or medical device sales.

E. Professional Organizations/Professional Societies/Awards

I have assumed national and international leadership roles in my areas of expertise. I am currently on the executive board of the *Society for Epidemiological Research*, to which I was elected by my peers. I am on the executive board of the *World Psychiatric Association Epidemiology and Public Health* section, and, in 2018, hosted the bi-annual meeting of the section at Columbia University. I serve on committees and boards for numerous other societies, including the *Research Society on Alcoholism* (program committee), *International Association of Population Health Science* (program committee), and *Society for Research on Adolescents* (dissertation award committee) among others, and each year I actively participate as a symposium chair and speaker on multiple workshops and roundtables at each of these meetings. In 2017, I was invited to join a National Academies of Sciences committee on accelerating the progress to reduce alcohol-impaired driving and contributed to the consensus report with evidence-based policy recommendations.[1] I have served on numerous NIH review committees for several study sections and institutes, and I joined the Epidemiology, Prevention and Behavior Research Review subcommittee of the National Institute of Alcohol Abuse and Alcoholism in 2019. Finally, I serve as Associate Editor of the journal *Drug and Alcohol Dependence* and as field editor for *Alcoholism: Clinical and Experimental Research*, both of which are highly regarded journals for original research on alcohol and drug use disorders and related harms.

My career achievements have been recognized with numerous awards. I was given the early career achievement award by three scientific societies (*Research Society on Alcoholism, American Psychopathological Association,* and *the World Psychiatric Association Epidemiology and Public Health Section*), as well as the *NIH Office of Disease Prevention Early-Stage Investigator* award, a competitive award recognizing two scholars per year, from any

NIH institute, who are poised to become leaders in the field. I have been and continue to be invited as a speaker nationally and internationally, with approximately 40 invited lectures, including 22 between 2017 and 2019.

II. OPINIONS

For the detailed reasons stated in this report, I intend to offer the following opinions in this case:

1. Medical use of opioids is associated with the development of opioid use disorder at higher rates than were reported by drug manufacturers. This assessment is based on standard principles and methods in the field of epidemiology, including confounding assessments, as well as consistency with biological knowledge, replication, dose response and length of opioid use among medical users.

2. Opioid use disorder is prevalent and disabling and occurs in approximately 8-12% of medical users; this estimate is likely an underestimate given that systematic assessment are not routinely done, and that tolerance and withdrawal after medical prescription cannot be diagnosed as opioid use disorder as of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a change that was industry-supported and relies on no statistical evidence of which I am aware.

3. The opioid supply increased dramatically in the United States beginning in the mid 1990s, and a direct consequence of the increased supply of opioids was an increase in the incidence and prevalence of opioid use disorder among both medical patients and non-patients (among non-patients, over-supply of opioids were diverted to illicit marketplaces).

4. The epidemic of opioid-related harm began with a rapid increase in prescription opioid overdose death; prescription opioids were identified as the primary opioid contributing to overdose mortality in the early years of the epidemiology (late 1990s and early 2000s); the epidemic then transitioned to heroin use being identified more frequently in opioid overdose deaths (while prescription opioids remained high), and since approximately 2013, synthetic opioids (primarily fentanyl) have been increasingly identified in opioid deaths. Fentanyl deaths did not increase uniformly in all locations; data from Cabell County indicate that fentanyl mortality began increasing after 2014. The expansion of prescription opioid distribution and availability laid the foundation for the increase in heroin and fentanyl deaths, and my report details the existing literature on the extensive evidence that prescription opioids modally precede heroin and fentanyl use, providing a basis for the opinion that prescription opioid use is a cause of subsequent heroin and fentanyl use, morbidity, and mortality.

5. The expansion of non-medical prescription opioid use would not have occurred without the widespread availability of prescription opioids that were originally dispensed supposedly (but not always actually) for medical uses, often in greater quantities and doses than needed, leaving a surplus of opioids that could be diverted for non-medical uses.

6. Prescription opioid use is causally associated with harm across the lifecourse, especially when it is initiated at critical developmental windows such as adolescence, and during fetal development due to maternal use.

7. Prescription opioid use is causally related to subsequent heroin use. Approximately 70-80% of individuals who began using heroin in the last two decades used prescription opioids before heroin, and while the proportion of prescription opioid users who progress to heroin use is relatively small, even small increases in the proportion who progress can explain the majority of increases in heroin use in the United States. Because the heroin supply has been contaminated with high-potency synthetic opioids (e.g., fentanyl) since approximately 2013, prescription opioid use is also causally related to the increase in synthetic opioid morbidity and mortality, since prescription opioids frequently precede the transition to heroin, including heroin contaminated with fentanyl.

8. Prescription opioid overdose increased exponentially in the United States in the past 20 years, and these increases strongly correlate with rates of prescription opioid supply for medical use both in

terms of geographic variation in supply as well as year-to-year variation, in both observational and quasi-experimental studies, providing an evidence base that supports this opinion that supply and availability of opioids caused an increase in the rate of prescription opioid overdose.

9. Prescription opioids cause accelerated and increased risk of harm when used in conjunction with other drugs such as other opioids, benzodiazepines, stimulants, and alcohol. When multiple drugs are listed as part of the contributing causes of death in an overdose death, the preponderance of evidence indicates that certain combinations of drugs, especially those that include opioids, are associated with multiplicative increases in risk of death; that is, without the prescription opioid, the individual would not have died when and how they did. Thus, multiple drugs present in a toxicology report are likely indicative of drug-drug interactions for which prescription opioids are attributed as a cause when listed as per the current available evidence in epidemiological and toxicological sciences. For these reasons, CDC and other authoritative sources correctly report overdose deaths that include prescription opioids as prescription-opioid deaths, even when additional drugs are identified.[2]

10. In the United States, almost 47,000 people in the US died of a drug overdose in 2018 for an opioid-involved overdose death rate of 14.6 per 100,000,[3] an almost 6-fold increase since 1999.[4–6] The beginning of the opioid crisis was marked by a rise in prescription opioid overdose deaths. West Virginia has the highest rate of opioid overdose in the nation, and among counties that report overdose rates, Cabell County has been among top ten counties with the highest overdose rate for the last four out of four years. In 2018, the last year of data available, I estimate that the prevalence of extra-medical opioid use is approximately 8-9% in the general population, underlying more than 100 people who have died due to opioid overdose. Approximately three quarters of those who use extra-medically, and those fatally injured by opioids, began their opioid use with prescription opioids.

11. In addition to fatal overdose, other consequences to the Cabell Huntington community affected by opioid oversupply include emergency department visits for overdose, increased burden in the treatment and chemical dependency provider system, opioid use disorder and opioid use among both adults and adolescents, and neonatal abstinence syndrome (NAS).

12. Prescription opioid and other opioid mortality disproportionately affected economically deprived areas; however, the available evidence indicates that economic conditions played a relatively small part in increased opioid-related morbidity and mortality. The driving force in increasing opioid-related morbidity and mortality was, and continues to be, access to and wide-spread availability of opioids.

13. Compared with other commonly used pain relievers, such as non-steroidal anti-inflammatory drugs (NSAIDs), the adverse health and addiction consequences are substantially and significantly greater from opioids than from NSAIDs, including for cardiovascular events, fractures, and falls, as well as poisoning and overdose.

To summarize, there is compelling evidence of harm from the oversupply of prescription opioids, both for medical users, and to non-medical users because of diversion. The Cabell Huntington community has experienced a high burden of harm due to opioids. These harms include opioid use disorders and overdose; these harms are greater than those associated with other pain relief drugs, and are causally related to additional harms from opioids including transition to heroin addiction.

III. METHODOLOGY

A. Definitions of methodological and substantive terms

Before detailing the scientific evidence that underlies my opinions, it is useful to describe a set of terms that I will be using throughout the report.

1. *The Cabell Huntington Community.* Throughout this report I will be describing epidemiological trends that relate to the county of Cabell in West Virginia, as well as the City of Huntington. I will note

specifically where data that are referred to are drawn from, but the inference for the report should be understood to relate to the overall community that is included in Cabell County and the City of Huntington.

2. *Prescription opioids*. Drugs approved for medical use in the United States for the control of moderate to severe pain that are either natural opiate analgesics derived from opium (morphine and codeine), semi-synthetic opioid analgesics (oxycodone, hydrocodone, hydromorphone, and oxymorphone), synthetic opioids (methadone), or synthetic opioid analgesics (e.g., tramadol and fentanyl).[7]

3. *Medical use of prescription opioids*. Medical use will refer to use of prescription opioids prescribed by a physician and used as directed by that physician exercising professional judgment acting within the scope of his or her license.

4. *Non-medical use of prescription opioids*. Non-medical use refers to both using prescription opioids more often or longer than prescribed, or use of prescription opioids without a prescription. These definitions are commonly used in large scale surveys of prescription opioid use in the population. For example, the National Survey on Drug Use and Health asks, "Have you ever, even once, used any prescription pain reliever in any way a doctor did not direct you to use it?" Examples given to respondents include use without a prescription, use in greater amounts, more often, or longer than prescribed, or use in any other way that a doctor did not direct. This question and similarly worded questions on other large-scale surveys are the commonly used assessment of non-medical prescription opioid use. Some reports also label this as "prescription opioid misuse"; however, I will use the term 'non-medical prescription opioid use' for consistency. Non-medical prescription opioid use is also referred to as *'opioid misuse'* in much of the literature, although definitions and measurement assessments differ in what is included as opioid misuse. For example, some measures of opioid misuse include using opioids for euphoria, or for the experience or feeling that using opioids caused, which could conflate some medical and non-medical reasons for use.[8]

5. *Opioid misuse*. For the purposes of this report, opioid misuse is synonymous with "non-medical prescription opioid use", and refers to use of prescription opioids in ways other than prescribed, including taking more than prescribed, or using prescription opioids that were not prescribed by a physician. As noted above, however, throughout this report I will detail the definitions that studies use when using the term "misuse" to highlight variation in the definition in the literature, and will primarily rely on the term "non-medical use of prescription opioids" when discussing the literature and findings related to use of opioids that is outside the medical oversight and prescription of a physician.

6. *Tolerance and physical opioid dependence*. Individuals who use opioids can develop tolerance to the medication. Tolerance develops when the endogenous opioid system acclimates to the medication and more is needed to produce the desired effects. Dependence on opioids also occurs in medical uses of opioids, in which more opioids are needed to achieve the desired effects (tolerance) and when the cessation of opioids produces symptoms of withdrawal and craving for opioids. Physical opioid dependence can occur even at low doses, but is increased with dose and duration of use. Physical opioid dependence does not currently meet the criteria for opioid use disorder, with changes to the DSM in the most recent revision. Physical opioid dependence is expected even when opioids are used medically; yet physical opioid dependence is clinically challenging, and increases the risk for transition of patients to opioid use disorders and addiction.

7. *Opioid use disorders*. Opioid use disorder is a diagnosis in the DSM, as well as the International Classification of Disease (ICD). It is important to point out from the outset of this description that opioid use disorder is distinct from the physical opioid dependence (defined above) that would be expected to occur with repeated administration of opioids. Medical use of opioids would be expected to produce symptoms such as tolerance (needing more opioids to achieve the same effect) and withdrawal (uncomfortable and painful physical and psychological symptoms during cessation of opioids). However, opioid use disorders involve a maladaptive pattern of use from which there are serious consequences in domains of functioning. The fourth version of the DSM was published in 1994, and included two diagnoses that together comprised opioid use disorders: opioid abuse and opioid dependence. Opioid abuse was diagnosed if there was "a maladaptive pattern of use leading to clinically significant distress or impairment" as indexed by at least one of four symptoms in a 12-month period, including recurrent failure to fulfill major role obligations (e.g.,

repeated absences from work, neglect of children), recurrent use in physically hazardous situations (e.g., driving under the influence), continued use despite social or interpersonal problems because of use (e.g., arguments with family, physical fights while intoxicated), and legal problems due to use.[9] Opioid dependence was diagnosed if there was "a maladaptive pattern of use leading to clinically significant distress or impairment" as indexed by at least three of seven symptoms in a 12-month period including tolerance (needing more opioids to achieve intoxication or desire effect, or diminished effect with continued use of the same amount of opioids), withdrawal (defined via a substance specific syndrome), using the substance in larger amounts or over a longer period than intended, persistent desire or unsuccessful efforts to cut down or control use, physical or emotional problems caused or exacerbated by use, excessive time spent in activities to obtain or use substance, and social/occupational/recreational activities given up in order to use.[9] Tolerance and withdrawal are symptoms of opioid use disorder; tolerance and withdrawal alone were excluded as a sole set of criteria for OUD diagnosis in DSM-5. This change to exclude individuals from diagnosis when based on tolerance and withdrawal alone underestimates the total burden of opioid use disorder in the population, given that psychometric and epidemiological evidence indicates that tolerance and withdrawal are valid indicators on the dimension of opioid use disorder (discussed further on Page 20 of this report). In DSM-IV, opioid abuse could only be diagnosed if the criteria for opioid dependence were not met. In DSM-5, opioid abuse and dependence criteria were combined for a single diagnosis of "opioid use disorder"; craving was added as a criterion (strong desires to use opioids); and "legal problems" was removed as a criterion. Diagnoses could be made at three levels: mild (2-3 symptoms); moderate (4-5 symptoms); and severe (6+ symptoms). Opioid use disorder diagnoses are sometimes made based on ICD-9 and ICD-10 criteria. These criteria overlap substantially with DSM criteria

8. *Addiction*. Addiction is a concept often synonymous with opioid use disorder, but is not a clinical term available for diagnosis in major nosology such as the DSM or the ICD. However, it is used frequently in the literature with various definitions, sometimes used to refer to physical opioid dependence, but most often to refer to individuals who use opioids non-medically for their euphoric effect, and/or those who exhibit harms due to opioids that include important social, occupational, physical, and relationship impairments due to non-medical prescription opioid use. Because addiction is not a well-defined clinical diagnosis, throughout this report I will detail how "addiction" is defined in studies that use the term, and will focus on opioid use disorder primarily when discussing the literature on opioid-related harms.

9. *Overdose*. An injury to the body caused by poisoning from excessive opioid use. Symptoms of an overdose include shallow breathing, weak pulse, loss of consciousness, and constricted pupils. An overdose can be fatal or non-fatal.

10. *Incidence*. Incidence, or incidence rates, refers to new diagnosis over a population at risk for developing the outcome during a specified time interval or per a specified time scale. For example, the incidence of opioid use disorder would be an assessment of newly developed cases among those who did not previously have a diagnosis across a specified time interval.

11. *Prevalence*. Prevalence, or prevalence rates, refers to the total number of cases over a well-described population. For example, the prevalence of opioid use disorder in a given year would be estimated as the total number of cases of opioid use disorder (both new and persistent) over the total population size.

12. *Relationship between incidence and prevalence*. Prevalence and incidence are both used to demonstrate total burden of harm for health outcomes in the United States. Prevalence rates provide essential information regarding the counts of cases and are a combination of new and existing over time, and can be used to assess risk factors and correlations. Because prevalence includes both new and existing cases, the prevalence of an outcome in a given population at a given time is estimated by the incidence rate multiplied by the average duration of the outcome (given a steady state population). Prevalence is critical for determining total burden of health outcomes, especially to assess surveillance of trends over time. Incidence of an outcome is critical for documenting emerging epidemics and the existence of new cases. The assessment of risk factors for incident cases is of interest because it can establish the extent to which exposures generate new cases of a health outcome; risk factors for prevalent cases combine risk factors for

new cases plus risk factors for cases that are chronic or un-resolving. This report will include information on both incidence and prevalence.

13. *Diversion*. Diversion of opioids has been defined in various ways across a variety of sources, including the transfer of opioids obtained through legal medical sources to the illicit marketplace. I will use a broader definition of diversion, which is consistent with numerous other scholars, which is that diversion occurs when opioids are diverted from their intended recipient, for example, when traded for monetary value, barter, or for no cost among family and individuals in a shared social network, or when sold for money by illicit dealers and traffickers. Opioids that are prescribed to individuals who knowingly deceive prescribers to obtain opioids, as well as by physicians who knowingly prescribe to individuals with no legitimate medical need, have a high likelihood of being diverted for non-medical use.

14. *Morbidity*. Morbidity refers to specific health conditions. In the context of this report, morbidity refers to conditions subsequent to opioid use such as opioid use disorder, non-fatal overdose and hospitalization, and other acute and chronic health conditions that arise from opioid use.

15. *Comorbidity*. Comorbidity refers to two or more specific health conditions of interest occurring concurrently. For example, individuals who have more than one drug use disorder simultaneously have comorbid drug use disorders.

16. *Systematic review*. A systematic review is designed to carefully summarize existing evidence on a specific topic. Systematic reviews provide defined search criteria in the peer-reviewed literature, report articles that were included an excluded with transparent criteria, and the relevancy of the studies included for generating conclusions about the research question under consideration. Judgments are made from systematic reviews about the quality of evidence that has been gathered, existing gaps in the research, and quantitative as well as qualitative assessments of the strength of the evidence. The purpose of a systematic review is to summarize the strength of the evidence for a particular topic. However, systematic reviews can be well or poorly executed, and their utility and reliability needs to be assessed carefully just like any other peer-reviewed publication.

17. *Meta-analysis*. Meta-analysis quantitatively combines evidence across studies to provide summary estimates for the association between exposures and outcomes. Meta-analyses take published and in some cases unpublished estimates from across studies and uses them to generate a summary estimate with more statistical power because of the combined effect across studies. Methods in meta-analysis allow researchers to weight studies based on quality or informativeness, such that studies that have a higher quality of evidence can be given a greater weight in determining the summary estimate. Meta-analyses are considered a higher level of evidence than single studies, because while single studies may have particular bias or confounding, a large number of studies analyzed together generally provide a more rigorous estimate of the true relationship. Studies that are included in a meta-analysis should be sufficiently similar to warrant summarizing estimates of magnitudes of association together, while simultaneously estimating heterogeneity in effect sizes across studies. As in the case of systematic reviews, meta-analyses can be well or poorly executed, and their utility and reliability needs to be assessed carefully just like any other peer-reviewed publication.

18. *Confounding*. Confounding occurs when risk factors that are causes of the outcome are unequally distributed between exposed and unexposed persons. Study estimates that are confounded do not reflect the true causal relationship between exposures and outcomes. For example, consider the relationship between prescription opioid use (exposure) and heroin use (outcome), which is evaluated in this report. Men are more likely to both use prescription opioids and to use heroin. Thus, the estimate of the relationship between prescription opioid use and heroin use is confounded by sex, and control for sex in statistical analyses of the relationship would be appropriate.

19. *Bias and misclassification*. Bias can arise in the study design and analysis of epidemiological studies from a variety of sources. Among the most pernicious forms of bias in epidemiological studies is information bias, also called misclassification. For example, a common source of misclassification in studies

of substance use disorder occurs when reporting on the presence of substance use disorder among a group of research subjects, any substance use disorder that is missed among research subjects would be characterized as misclassification. With regard to opioid use disorders, the presence of disorder is often underestimated due to misclassification of opioid dependent individuals as non-dependent. Misclassification is magnified when opioid use disorders are not assessed with structured, validated instruments for measurement of opioid use disorder, or with objective assessments of the presence of opioids and other drugs through urine toxicology. Further, misclassification has been assessed in vital statistics designations of causes of death for which opioids may be involved.[10] Death certificate procedures vary by state and local region within state, in terms of the training of the individual completing and certifying the death certificate, and with regard to the quality and completeness of the information presented on the death certificate. However, it is worth noting that the high-quality procedures conducted to investigate and designate overdose deaths in West Virginia have been documented. Drug overdose death data have been reviewed and maintained by the West Virginia Department of Health and Human Resources Bureau for Public Health along with the Office of the Chief Medical Examiner with examination of toxicology results and investigations as reported on death certificates since at least 2001.[11] Further, as outlined in reports and peer-reviewed publications,[11–13] the West Virginia Office of the Chief Medical Examiner created a forensic drug database in 2005 to track and record information on overdose. Overdose deaths are designated based on forensic investigation and pathology, including toxicology and autopsy, preceded by drug screening which is conducted in all medical examiner-referred deaths. Toxicology is then confirmed through tissue sampling with high-quality and high-validity tests for the presence of a wide range of opioids. Thus, data on overdose from West Virginia is of high quality.

B. What role does epidemiology play in describing opioid-related harm?

Epidemiology is the "science of understanding the causes and distributions of population health."[14] To understand causes and distributions, epidemiologists examine the dynamic nature of populations and how health and disease arise within them, as well as the conditions that shape population health over time and space, including policies, practices, and politics that create conditions that improve or deteriorate population health. Whereas a physician examines each patient that enters her clinic, asking what caused a particular health outcome for this particular patient, an epidemiologist looks over the landscape of a population across time to determine why the burden of a particular health outcome is greater or worse in some areas, at some time points, and among some subgroups, and queries what in the social, political, and environmental landscape create the distributions and their changes over time.

Epidemiology has played a key role in understanding the increases in opioid use and related harm in the population. A central role for epidemiology is surveillance. Using a variety of methods, epidemiologists examine the incidence and prevalence of opioid use, non-medical opioid use, and consequences of use such as opioid use disorders, overdose, and neo-natal abstinence syndrome across time and place, as well as factors that influence opioid prescribing, use, and misuse. Epidemiological studies have documented changes in the incidence and prevalence of these outcomes across time, heterogeneity in the incidence and prevalence by state and county, and correlations with factors such as availability and access of opioids, individual-level risk factors, and policy changes. Further, epidemiological studies are critical in documenting the longitudinal short- and long-term consequences of inter-individual variation in risks associated with opioid use. That is, epidemiological studies compare individuals with and without specific opioid use patterns to determine the longitudinal associations between use and health and mortality. Epidemiologists are particularly trained to control for and examine confounding, which is commonly used to mean common causes of an exposure and an outcome that are being assessed. When confounding is present, groups are not comparable to each other on causes of the outcomes other than exposure. For example, individuals who do and do not use opioids (both medically and non-medically) may have different underlying risk factors for long-term health and mortality risks, and thus the science of epidemiology involves testing the extent to which relationships between exposures and outcomes are robust to statistical controls for these risk factors. Epidemiologists use a variety of methods to control for confounding in estimates, including statistical controls in regression models, propensity scores estimation, randomization, and quasi-experimental methods such as instrumental variable analysis. In summary, the role of epidemiology in describing opioids is to quantify the extent to which use and

harms associated with use are changing over time, the determinants of those changes, as well as individual-level risk factors for non-medical use and harm.

Key to epidemiological assessments is the concept of risk factors. Risk factors are variables that, when present, increase the frequency with which an outcome occurs, but need not be necessary or sufficient for the occurrence of the outcome to be fully determined. A useful example is that of cigarette smoking and lung cancer. It is now widely accepted that cigarette smoking is a cause of lung cancer. However, not all cigarette smokers will develop lung cancer (thus, cigarette smoking is not sufficient to cause lung cancer in and of itself), and not all lung cancers occur among smokers (thus, cigarette smoking is not fully necessary to cause lung cancer). Yet, cigarette smoking increases the risk that lung cancer will occur, and thus it is considered a cause of lung cancer if there are cases of lung cancer that would not have occurred in the absence of cigarette smoking. I will apply the same "risk factor" framework to my assessment of the causes of the opioid crisis, considering factors to be causes of opioid use disorders, overdose, and related harm if some cases would not have occurred in the absence of prescription opioid use. This framework does not preclude or ignore that addiction and related harms are multi-factorial in their etiology, but rather asks whether there are cases for which the outcome would not have occurred without the presence of prescription opioid use.

C. Methodology for review of the evidence

I undertook a review of the evidence to assess the impact of opioid sales and distribution in the United States, as well as harms incurred from opioid use, opioid use disorders, diversion, and transition to heroin on opioid-related outcomes and among families and children. I also estimate unmet need for treatment in the Cabell Huntington Community.

1. Literature search methodology

My review of the evidence began with a literature search. In order to conduct this literature search. I relied on methodology that is considered standard in the scientific process, as outlined below.

First, I used search terms in the peer-reviewed literature related to the areas of my literature search. For this I used PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), a search engine produced and maintained by the US National Library of Medicine National Institutes of Health. Full texts of scientific articles produced in the searches were available by subscription through my faculty appointment at Columbia University. Search terms were entered into the search bar, and titles were then reviewed for relevance to each particular topic. Full- texts were then reviewed to determine if there was original data and information within each specific category that related to topics covered in the expert report. Full-text articles in journals that are indexed in PubMed are considered to be reputable; journals that are indexed by PubMed have long histories of publication, and are included only if they meet well-recognized standards including editorial oversight by recognized experts in the field as well as peer-review by experts.

Peer-review is considered to be the gold-standard of the scientific process; peers are experts in the field who evaluate each submitted paper for flaws in design and logic and make quality assessments. However, while peer-review is an important component of the scientific process, peer-review is not sufficient alone to establish quality and validity of a scientific study. Limitations in the peer-review system have long been documented in the scientific literature, including that inadequate study design and statistical analysis flaws go unnoticed by peer-reviewers,[15] publication biases lead to scientific studies with statistically significant results more likely to be published and cited than studies with null results,[16] incorrect and inaccurate reporting of study outcomes and results,[17] and the pernicious influence of conflicts of interest among study researchers that leads to bias in the conduct and reporting of research.[18] For example, the British Medical Journal found that financial ties of study investigators were associated with a 3-fold increase in positive study results, based on analysis of 190 clinical trials that were published in 2013.[19] While the scientific literature has made advances in the peer-review system through rigorous development of reporting guidelines, more clarity and specificity in the reporting of conflicts of interest, and the inclusion and compensation of editors who additionally review papers for quality, peer-reviewed studies should still be rigorously evaluated when deciding whether to cite them for a particular piece of evidence. In this report I have included studies assessed by peer-

review and done additional review of the articles based on my own expertise in order to discern whether they meet quality benchmarks. As an associate editor for multiple scientific journals, I have over a decade of experience evaluating the quality of the scientific literature for publication. I have served as a peer reviewer for hundreds of scientific papers in the field of substance use and substance use disorder epidemiology, and I am thus well qualified to evaluate the literature for papers that demonstrate a sufficient level of quality to be relied upon in my review of the evidence.

Second, within full-text reviews, additional studies that were relevant to each topic were identified based on the reference lists and citations of articles identified by PubMed search. Reference lists were reviewed and additional articles extracted based first on title review for broad relevance to the topic of study. Then, full texts were studied and evaluated, and included in the evidence review if the article contained original information that was reliable and relevant to the topic under study.

Finally, I also studied and evaluated the non-peer-reviewed "gray" literature relevant to the topics under study. Specifically, I reviewed government and agency reports from the following: Centers for Disease Control and Prevention, Substance Abuse and Mental Health Services Administration, and Agency for Healthcare Research and Quality. These reports included assessments of time trends in opioid poisoning and overdose, rates of opioid use disorder, and hospitalizations for opioid-related causes. Other gray literature was included in my evidence review based on review of reference lists from PubMed searches when relevant to the topic of study. I have also, where appropriate, considered new and novel data contained in Letters published in top tier journal where submissions are peer reviewed. I also considered materials provided by the Plaintiff's counsel, and they are included in the materials considered list.

2. Levels of evidence evaluated

Throughout this report, I make assessments of the rigor of the evidence that has been used to support conclusions and opinions. There are two general categories of studies that I will include in this report: the first are studies that examine associations, and the second are studies that examine trends over time.

With regard to studies that examine associations, I considered the following levels of evidence. First, I considered randomized controlled trials to be a high level of evidence, given that the possibility of confounding and bias to influence the results is most likely to be mitigated in randomized controlled trials. For example, in sections on evidence for opioid use disorder after medical use of opioids, I included randomized controlled trials that included information on outcomes such as 'aberrant drug use behavior'. However, for many of the associations reported in this statement, randomized controlled trials are unfeasible or unethical, or uninformative for the question of interest. For example when assessing the transition from prescription opioid to heroin use, it is highly unethical and would never be considered to randomize individuals to high levels of prescription opioids in order to observe the transition to heroin once prescription opioids were tapered. Indeed, for much of the literature cited in this report, randomized controlled trials would never be conducted. Furthermore, randomized controlled trials are not *de facto* strong evidence, as publication bias, conflicts of interest, specifics of the study design, study population assessed, outcome measurement, study duration, statistical power, and rigor of statistical analysis should all be considered when evaluating a particular randomized controlled trial for the level of evidence that it brings to a particular study question. For example, many randomized trial of prescription opioids are uninformative for relevant questions of opioid use disorder incidence due to the lack of systematic measures of opioid use disorder and psychiatric diagnoses, exclusions from participation in trials among those with prior substance use disorders, and low dose/short duration of opioid exposure. In the circumstances that randomized controlled trials were not available, rigorous, or applicable to the question at hand (e.g., risk of opioid use disorders among those prescribed opioids), I considered meta-analysis and systematic reviews to be high levels of evidence, and cite them as well as discuss their findings when they are available. Systematic reviews and meta-analysis are considered high levels of evidence because they quantitatively and qualitatively assess the overall body of the literature and provide quality assessments that weight evidence, but are subject to limitations if not conducted rigorously and are not taken as strong evidence without careful review. I consider studies that had prospective follow-up of patients or participants, a well-described strategy for statistical control of confounders, and well-

designed comparison groups to be the next level of evidence. Prospective follow-up is an important study design because it reduces biases in epidemiological studies from retrospective reporting of symptoms or events. Further, statistical controls are necessary to overcome the potential for bias from confounding. Prospective studies often involve comparison groups (e.g., prescription opioid users and a comparison group of non-prescription opioid users). Study designs with comparison groups provide evidence regarding opioid-related harm that is over and above harm in patient and general population samples across varying levels of opioid exposure. Studies of patient populations without comparison groups, however, are also informative particularly for research questions germane to the prevalence of opioid use disorders and related harm among patients prescribed opioids (especially high doses in long duration), as well as questions related to the proportion of drug users who previously used prescription opioids. Well-designed studies of single populations without explicit comparison groups are thus also considered by me as relevant evidence for characterization of prescription opioid-related harms.

With regard to studies that assess trends over time, I considered three data sources to be the highest levels of evidence. First, I relied on death records that are collected and harmonized by the national vital statistics surveillance system. While death records can have misclassification of causes of death, they are considered by experts to be a reliable indicator of national and local burden of specific causes of death, especially when examining trends over time. Second, I relied on data sources with a national reputation for transparency in reliability and validity that assess hospitalization and other clinical records, such as large electronic health databases, as well as national studies such as the National Inpatient Sample. Again, while such records can include misclassification, data sources gathered from reputable organizations such as the Agency for Healthcare Research and Quality include reliability and validity assessments that allow the researcher using them to be able to draw conclusions based on the best available evidence. Third, I relied on survey data that is routinely collected in the general population of households in the United States over time. Surveys are essential parts of surveillance, given that many cases of substance use disorder do not come to clinical attention, and thus relying on clinically ascertained records can give a biased assessment of trends and burden in the population. Survey data source methodology involves clustered sampling so that samples are representative of the entire United States, and respondents are interviewed with validated instruments that are designed to elicit diagnoses and information with maximum accuracy in the survey context. Generally, I do not include surveys that are not representative of the population, as they are not strong evidence for an assessment of the total burden and trends over time.

IV. DETAILED DISCUSSION OF OPINIONS AND REASONS AND BASES FOR THEM

A. Distribution, sales, and marketing of opioids increased in the 1990s

There is voluminous evidence regarding the increased distribution, sales, and marketing of opioids beginning in the 1990s. This evidence is the subject of other expert reports, and I will not repeat all of that evidence here. Instead, I will summarize some points for context. Opioid pain relievers became an increasingly widely-used option starting in the mid 1990s, particularly for chronic non-cancer pain, a use that had rarely been seen previously. Estimates from the Automation of Reports and Consolidated Orders System (ARCOS), which tracks prescription distribution and sales, indicate that prescription opioids were dispensed at an estimated 96 mg per person in 1997, and increased to 700 mg per person by 2007 (greater than 600% increase).[20,21] In 1995, the year OxyContin entered the market, the number of opioid prescriptions filled in the United States increased by 7 million, and continued to increase over the next two decades before peaking in the fourth quarter of 2012 at 62 million prescriptions dispensed.[22,23] From 1997 to 2002, prescriptions for OxyContin for non-cancer pain increased from approximately 670,000 in 1997 to about 6.2 million in 2002.[24] The increase in opioid prescribing was driven by a multitude of factors, including direct marketing to physicians using data that underestimated opioid use disorder risks in patients, which I will detail in Section B. Evidence shows that pharmaceutical marketing of prescription drugs increases prescribers' likelihood of prescribing the marketed drug in the future.[25,26] That is also true for prescription opioids; as a result, increasing marketing of opioid drugs led to increased sales of the marketed drugs.[27–29]